pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pazopanib (Votrient) for Soft Tissue Sarcoma

November 29, 2012

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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TABLE OF CONTENTS

DISCLAIMER & FUNDING..... i

INQUIRIES..... ii

TABLE OF CONTENTS..... iii

1. ECONOMIC GUIDANCE IN BRIEF..... 1

1.1. Background..... 1

1.2. Summary of Results..... 2

1.3. Summary of Economic Guidance Panel Evaluation..... 3

1.4. Summary of Budget Impact Analysis Assessment..... 5

1.5. Future Research..... 5

2. DETAILED TECHNICAL REPORT..... 6

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3. ABOUT THIS DOCUMENT..... 7

REFERENCES..... 8

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by GlaxoSmithKline (GSK),** compared pazopanib to placebo for patients with advanced soft tissue sarcoma (STS). This patient population reflects patients from the PALETTE trial (Van der Graaf et al. 2012). Pazopanib is administered orally. The PALETTE trial was a randomized, placebo-controlled Phase III study in patients with advanced STS (excluding gastrointestinal stromal tumour, GIST, and adipocytic sarcoma) who had received prior chemotherapy or were unsuited for such therapy. Current standard of care in Canada for advanced STS include doxorubicin (DOX) alone, DOX combinations such as mesna/adriamycin/ifosfamide/dacarbazine (MAID), DOX + ifosfamide (IFOS) and adriamycin + dacarbazine for first line treatment (administered intravenously). Second-line treatment includes IFOS (if not used first line), dacarbazine and gemcitabine +/- docetaxel (administered intravenously).

According to the pCODR Clinical Guidance Panel (CGP), this comparison was appropriate.

Patient advocacy groups considered the following factors important in the review of pazopanib, which are relevant to the economic analysis: improvement in a patient's quality of life and survival and an accessible treatment that will enable them to continue to work and maintain a normal family life. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

- The submitted economic analysis explicitly considered improvements in quality of life by applying utility scores and measuring outcomes in quality-adjusted life years. The quality of life information was collected from the PALETTE trial.
- The model has not considered whether pazopanib will enable patients to spend more time working or with family – the model adopts the perspective of the publicly funded health care system which is appropriate for pCODR because drug funding recommendations must be considered from a health system perspective.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for pazopanib, and which are relevant to the economic analysis: potential for pazopanib to be used in other treatment settings, oral dosing and administration, and use of pazopanib in patients who failed previous chemotherapy. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

- Oral administration of pazopanib was not explicitly considered in the submitted model as pazopanib compared with placebo, not intravenous treatments.
- Evidence to support use of pazopanib in patients unsuited for previous chemotherapy is lacking. This was not explicitly considered in the submitted model.

At the list price, pazopanib costs $41 per 200 mg tablet. At the recommended dose of 800 mg per day, the average cost per day in a 28-day course of pazopanib is $164 and the average cost per 28-day course is $4,592. At a lower submission price, pazopanib costs $37 per 200 mg tablet; and at the recommended dose of 800 mg per day, the average cost per day in a 28-day course of pazopanib is $148 and the average cost per 28-day course is $4,144.

1.2 Summary of Results

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $146,950/QALY and $167,782/QALY when pazopanib is compared to placebo. This estimate is based on reanalyses conducted by the Economic Guidance Panel using the submitted price and the model submitted by GSK.

The incremental cost-effectiveness ratio (ICER) was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔQALY or ΔLY). The Economic Guidance Panel's best estimate of:

- the extra cost (ΔC) of pazopanib is between $25,555 and $29,178. Costs included drug costs and healthcare costs associated with routine follow-up for patients receiving active treatment, disease progression, and routine health care resources involved in best supportive care. Costs associated with management of serious adverse events were also considered.
- the extra clinical effect (ΔQALY) of pazopanib is 0.174 QALYs (9.05 weeks). Key clinical effects included progression-free survival and overall survival estimates from PALETTE study (Van der Graaf et al., 2012), a randomized controlled trial comparing pazopanib with placebo. The biggest influence on QALYs was the estimate of survival following tumour progression and time horizon.

This range is based on Economic Guidance Panel reanalyses that modelled pazopanib using the **post progression-based survival function (PPS-Based Analysis)** and assuming the model's time horizon to be shorter than the proposed lifetime time horizon modelled by the manufacturer. The assumption that the time horizon should be reduced was supported by the pCODR Clinical Guidance Panel.

- The upper estimate of the range (ICER of $167,782) assumed that the time horizon of the model was reduced to 5 years (the expected duration of clinical benefit suggested by the pCODR Clinical Guidance Panel) versus the 10 years modelled by the manufacturer in addition to increasing the dose intensity to 100%. The extra costs associated with pazopanib were $29,178 and the extra QALYs associated with pazopanib were 0.174.
- The lower estimate of the range (ICER of $146,950) assumed that the time horizon of the model was reduced to 5 years (the expected duration of clinical benefit suggested by the pCODR Clinical Guidance Panel) versus the 10 years used by the manufacturer. The extra costs associated with pazopanib were $25,555 and the extra QALYs associated with pazopanib were 0.174.

The Economic Guidance Panel's estimate differed slightly from the submitted estimates. This is primarily because in the manufacturer's base case analysis, using the partitioned-survival analysis approach, progression and survival are modelled independently; there is no direct assessment of a patient's risk of dying before tumour progression and a patient's risk of dying after tumour progression; implicitly assumed that a patient's risk for dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state; and that progression-free survival and overall survival were extrapolated using short term data. The Clinical Guidance Panel determined that assuming similar risks of dying pre and post progression did not appropriately reflect realistic clinical practice and that survival benefits would not be anticipated beyond duration of 5 years. Therefore, in the Economic Guidance Panel reanalyses, when the post-progression based survival analysis was used instead, and the time horizon was shortened to align with clinical data, extra QALY gains for pazopanib are lower and lead to an increase in the extra healthcare-associated costs for pazopanib.

According to the economic analysis that was submitted by the manufacturer, when pazopanib was compared to placebo using a partition-survival analysis over a 10-year time horizon:

- The extra cost (ΔC) of pazopanib is $21,083. Incremental costs for pazopanib are based on a model where survival and progression are modelled independently and assuming that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state, which the CGP considered as inappropriate.
- The extra clinical effect (ΔE) of pazopanib is 0.128 QALYs. This was largely driven by the assumption that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state, which the CGP considered as inappropriate.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC/ΔE) was **$165,246 per QALY**.

In addition, according to an economic analysis that was submitted by the manufacturer, pazopanib was compared to placebo using a post progression-based survival analysis approach over a 10-year time horizon:

- The extra cost (ΔC) of pazopanib was $25,635.
- The extra clinical effect (ΔE) of pazopanib was 0.178 QALYs.

So, the Submitter estimated that, based on PPS-based analysis, the incremental cost-effectiveness ratio (ΔC/ΔE) of pazopanib was $143,778 per QALY.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The manufacturer submitted an economic evaluation using two different modelling approaches; partitioned-survival based analysis and post-progression based analysis. In the partitioned- survival analysis, survival and progression are modelled independently. As a result, a significant proportion of life expectancy gain is derived from extrapolated data not actual data, biasing results in favour of pazopanib by overestimating increases in the clinical effects for pazopanib versus placebo. In other words, the model implicitly assumed that patients continued to benefit from the drug as if there was carry-over beneficial effect of the drug even after tumour progression has occurred and the drug has been stopped. The Clinical Guidance Panel determined that assuming such benefit effect may not be a realistic expectations and that survival benefits would not be anticipated at 5 years with this treatment. Using the post-progression based analysis or 'Markov cohort analysis', survival functions for PFS and post-progression survival are used to derive the transition probabilities and to calculate the survival function for OS; therefore, it is assumed that the mortality rate from cancer is a function of time and is influenced directly by the increasing proportion of patients in the post-progression state. The Economic Guidance Panel estimate is based on a reanalysis which utilized the PPS-based analysis approach while assuming that the time horizon of the model was reduced to align with the short term data for progression free survival and overall survival.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Yes. Based on patient advocacy group input, patients considered the following factors important in the review of pazopanib and which were relevant to the economic analysis: improvement in a patient's quality of life and enabling them to spend more family time. These factors were addressed in the economic analysis when possible and appropriate.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

The manufacturer submitted a partitioned-survival based analysis in which patients transitioned between three health states; alive and progression-free, disease progression and death. Transition rates between these health states were determined by progression-free survival and overall survival estimates from PALETTE study (Van der Graaf et al., 2012). However, by using the partitioned-survival analysis approach, survival and progression are modelled independently and it is implicitly assumed a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state. This was rectified using the manufacturer's second modelling approach, the PPS-based survival analysis, where overall survival is derived from post-progression survival rather than vice versa.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that had an important effect on the results?

In the submitted base-case analysis, a partitioned-survival analysis approach was used that modelled survival and progression modelled independently; there is no direct assessment of a patient's risk of dying before tumour progression and a patient's risk of dying after tumour progression. The submitter assumes that over a 10-year period a patient's risk of dying following tumour progression would be improved with pazopanib even though treatment with pazopanib would have been stopped early in the 10-year time period. This modelling approach implicitly assumed that patients continued to benefit from the drug as if there was carry-over beneficial effect of the drug even after tumour progression has occurred and the drug has been stopped. The time horizon of the data from the clinical trial, PALETTE, is shorter in comparison with the 10 year time horizon of the model. Based on the clinical data currently available and expected estimates of biological plausibility, the Clinical Guidance Panel suggested that it was unlikely there would be any survival benefit accrued beyond five years with this treatment. Therefore, assumptions around extrapolation using short term data could have a pronounced effect on clinical effect estimates. Overall, this has an impact on the cost-effectiveness estimates and the Economic Guidance Panel conducted reanalyses to address these limitations by using a post-progression-based survival analysis approach, which led to higher estimates of the ICER.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

Yes – this is a well designed study with mostly appropriate estimates in the submitted analysis.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The manufacturer submitted a budget impact analysis that was not specific to any Canadian public drug plan. The analysis estimates the increased costs for the three years subsequent to the listing of pazopanib for metastatic STS. The key variables included in the manufacturer's budget impact analysis are: prevalence of STS in Canada, treatment cost, proportion of population covered by a provincial public drug plan, and the market share for those who are covered. The factors which most heavily influenced the budget impact analysis are the proportion of metastatic STS patients eligible for public coverage and the proportion of these patients who would use pazopanib if available rather than the currently used treatments.

What are the key limitations in the submitted budget impact analysis?

The model structure of the budget impact analysis was appropriate. The key limitations of the submitted budget impact analysis relate to the estimates of the current mix of available therapies in Canadian patients which were unavailable and were based on data for patients participating in the SABINE study; the distribution of treatments received in this study may not match those amongst STS patients in Canada. Another limitation is the estimates of market share and market expansion with pazopanib which were based on the Votrient Demand study. This study did not included Canadian physicians amongst the survey participant; the utilization of pazopanib in Canada might therefore differ from that projected based on this study.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

The economic evaluation of pazopanib could have been improved by including long term efficacy and survival data from clinical trials.

Is there economic research that could be conducted in the future that would provide valuable information related to pazopanib in this context?

If pazopanib becomes a standard treatment option for patients with metastatic STS, an assessment of effectiveness and cost-effectiveness of treatment sequences of pazopanib and other treatments for metastatic STS would also provide a more accurate reflection of real-world cost-effectiveness and may improve estimates of budget impact.

2 DETAILED TECHNICAL REPORT

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3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Sarcoma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of pazopanib for STS. A full assessment of the clinical evidence of pazopanib for STS is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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